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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,513	BOTH ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and argument of 3/7/08 are entered.

Claims 2 and 4-28 are cancelled.

Claim 1 is amended.

Claims 29 and 30 are newly presented.

Claims 1, 3, 29 and 30 are presently pending and considered.

Claim Status, Cancelled Claims

In light of the cancellation of Claims 2 and 4-28, all rejections and/or objections to such claims are rendered moot, and thus, are withdrawn.

Claim Objections

Claims 1 and 3 are newly objected to because of the following informalities:

Claim 1 recites "probain promoter" as well as "purine nucleoside phosphorylase (PND) enzyme". While it is clear that Applicant is actually attempting to claim the probasin promoter, as no probain promoter can be found in the art by the Examiner, and it is not supported by Applicant's specification, and while it is further clear that Applicant may provide any name they wish for the purine nucleoside phosphorylase, Applicant is requested to amend the claim to recite "probasin promoter" and "purine nucleoside phosphorylase" to avoid confusion on the part of the Artisan.

Claim 3 is objected to for depending from an objected-to claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 - clarity

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 29, 30 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons necessitated by amendment.

Claims 1 and 29 each recite the limitation "a transcriptional enhancer sequence (PSME)". While the limitation within the parentheses typically indicates a short-hand name for the limitation claimed (i.e., PSME would be short-hand for a transcriptional enhancer sequence), the specification teaches that PSME is a specific transcriptional enhancer sequence, specifically it is meant to refer to the prostate specific membrane enhancer (e.g., p. 8, paragraph 2). Hence, it is unclear whether this limitation, i.e., "(PSME)", is meant to further limit the transcriptional enhancer sequence to the PSME described in the specification, or is simply provided as a short-hand label for any transcriptional enhancer, or lastly, is provided in a manner to indicate an enhancer such as the PSME enhancer. Either way, the limitation as written would be unclear to the Artisan for its scope encompassed, and hence, the claims are rejected for lack of clarity. Further, in order provide the broadest reasonable interpretation; the claimed limitation is interpreted to encompass any transcriptional enhancer sequence.

Claims 3 and 30 are rejected for depending from a rejected base claim, and not overcoming the lack of clarity in such base claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 29 and 30 remain and/or are newly rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-57 of U.S. Patent No. 7,019,030 to Setiawan, and/or claims 1-51 of US Patent No. 6,020,172 to Both, and/or claims 1-18 of U.S. Patent No. 7,037,712 to Both, separately and/or in combination, and further in view of U.S. Patent No. 6,159,467 to Chung, et al., and Khatri, et al. (1997) Virology, 239: 226-37, as further evidenced by Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67), Qiu, et al. (1998) Human Gene Therapy, 9(4): 507-20 (ABSTRACT ONLY); and Hodgeson

(1996) Nature Biotechnology, 14: 339-342; Song, et al. (2000) Oncology Reports, 7(1): 119-24; Porter, et al. (1998) Journal of Virology, 72(6): 4832-40; Saeki, et al. (1997) Human Gene Therapy, 8(17): 2133-41; Kaneko, et al. (1996) Cancer Letters 107: 211-15; Kaneko, et al. (1996) Cancer Letters, 105: 39-44; Shimura, et al. (1985) Virology, 144(1): 268-72, and further in view of Martiniello-Wilks, et al. (1998) Human Gene Therapy, 9(11): 1617-26 (ABSTRACT ONLY), and further in view of U.S. Patent No. 6,197,293 to Henderson, et al, for reasons of record, as modified below due to the amendments.

The Setiawan patent is drawn to atadenoviruses, including OAV623, and further a composition of a cationic lipid, which may be CS87, or members of the genera including CS60. The patent teaches that these lipids may be used as a cyroprotectant, however, the Art above, teaches the other aspects of the claims (i.e., use of the cationic lipids to increase transfection efficiency), as is shown throughout the Art rejections, below.

The Both '172 patent teaches and claims ovine adenoviruses, the prodrug/enzyme combinations claimed, the promoters claimed, to, *inter alia*, treat cancers.

The Both '712 patent teaches and claims the generic atadenoviruses and the OAV287 atadenovirus which is the prototype upon which all other modifications are made in the art.

Hence, in light of any single patent and/or any combination of the patents, and further in view of the Art cited, it would have been obvious to make the claimed inventions. The Artisan would have found it simple substitution of one structure for an equivalent one, thereby producing predictable results.

Response to Argument - DP rejections

Applicant's argument of 3/7/08 has been fully considered but is not found persuasive.

Applicant argues that the amendments to the claims, and the Arguments provided to the other rejections previously proffered, render the ground of rejection moot (p. 5, paragraph 4).

Such is not persuasive. The claims and supporting specifications provide a demonstration that embodiments are encompassed in each patent, either alone or in combination, along with the demonstrations in the Art, such that a double-patenting rejection is proper. Applicant's aversions that limitations are missing and hence overcome the rejections are incorrect, as all the limitations are present, and Applicant has not indicated how any limitation is missing the rejections above. Still further, there are no unexpected results that the Examiner has found. The Art predicts the treatment (Further analysis of such may be found in the response to the arguments against the Art under obviousness). Lastly, with regard to the broad implication that the number of references is too large, and simply amounts to hindsight reconstruction, the findings in KSR v. Teleflex have specifically stated that the number of embodiments must be infinite in order to overcome obviousness-type rejections, and further, any rejection under obviousness type reasoning necessarily requires a form of hindsight reconstruction, as the Examiner must know the limitations which are to be rejected. However, the Examiner at no point cites teachings within Applicant's specification to arrive at the same subject matter, and hence, it is argued that impermissible hindsight was never applied in the rejections.

Claim Rejections - 35 USC § 112 – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 29 and 30 remain and/or are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for direct administration to the tumor, does not reasonably provide enablement for any form of administration, for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant's claims encompass any form of administration to transform cancer cells in a subject, and thereby express a suicide gene which converts a subsequently administered prodrug, thereby killing the cancer cells.

The problem of targeting the tissue is one of the biggest problems in the Art with regard to therapeutics in gene therapy techniques. With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is

unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression … The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Still further, in the case of the liposome co-administered, the adenovirus will have even better tropism for many tissues (e.g., Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67) and hence, if not directly administered, the viruses would be predicted to transform many other cell tissues before even reaching the target tumor tissue, and therefore, the prodrug would kill distinct tissues and possibly even the subject, before therapy is even affected.

Applicant's specification provides evidence of increased transformation efficiency (EXAMPLES) however, there is no specific direction, guidance or examples, which would allow the Artisan to reasonably predict that any particular form of administration, besides direct administration would allow for specific targeting of tumor tissues, allowing enough protein to be produced, and not killing off other tissues.

Hence, outside of direct administration, the Artisan would not reasonably predict any other form of administration would be efficacious. Hence, the Artisan would have to experiment with the other forms of administration in any particular cancer and subject to determine which forms of administration would affect therapy without killing the patient. Such experimentation is undue because it amounts to inventing the breadth of Applicant's claimed invention for Applicant.

Hence, the claims are not enabled for any form of administration besides direct administration to the tissue. The composition claims are included in the rejection, as they are

commensurate with the method claims and as such, it is apparent that they must be enabled for the same scope.

Response to Argument – enablement

Applicant's argument of 3/7/08 has been fully considered but is not found persuasive.

Applicant argues that there is no evidence provided by the Examiner to argue that the composition delivered by any other means than direct injection, and hence, the rejection is improper (p. 6, paragraph 2).

Such is not persuasive. The Examiner has cited Art demonstrating the difficulty of targeting tissues is gene therapy techniques, and further demonstrated that there is reasonably expected to increased transformation of any tissue due to the compositions utilized, and hence, not only would be difficult to reach the tissue in large enough numbers, but such numbers are further lowered by the increased transformation efficiency, increasing the likelyhood transformation of tissues encountered on the way to the tumor tissue. It appears illogical to state that no evidence for the argument was (and is again) provided.

Applicant argues that the methods do not include a method of delivery and therefore were improperly rejected (Id.).

Such is not persuasive. Applicant's method clearly requires delivery (e.g., Claim 1, reciting "delivering to the solid tumor"). Hence, the Artisan would not determine such to be direct injection, but any form of administration which yields the required transformation. The Examiner's arguments further demonstrate that other than direct injection, no other form of administration is reasonably predicted to be efficacious.

Applicant states that page 10 of the specification, lines 21-24 supports methods of administration beyond that of direct administration, and delivery to the airway to deliver to lung tumors, and broadly argues that many methods of non-direct delivery are known in the Art, and hence, the rejections are improper (p. 6, paragraph 3).

Such is not persuasive. The cited specification paragraph only discusses DNA vaccination methods for tumors, which are wholly distinct from suicide genes, as it simply requires expression of the antigens/cytokines, not the expression in the tumor tissue itself. With regard to aversion that specific viruses were delivered through airway passages, to lung tumors, such may be a specific embodiment, but such is not what is claimed, and further, the specific probasin promoter is active for prostate tumors, which are most definitely located in regions other than the lungs (it is noted that the first metastases of most tumors is to the lung, however, Applicant's methods are not drawn to treating metastases, but specifically to cancers in which the probasin promoter is active, which the specification teaches is prostate tumors, and hence, the Artisan would not find simple delivery to the lungs to enable the breadth of such prostate tumors, which are well known in the Art to metastasize into other tissues, such as bone). Moreover, the increased breadth of tissues is not explained such that the Artisan would not reasonably predict delivery by any method to the tissue, as it would be reasonably predicted to have increased transformation of other tissues on the way to the tumor, precluding transformation of the tumor. All of this has been argued either directly or indirectly, as above. Hence, the Artisan would still not find the claims enabled for their breadth.

Previous Art Rejections of Record Which are Withdrawn

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections on basis methods/compositions

In light of the amendments, the rejections of Claims 1 and 3 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,159,467 to Chung, et al., and Khatri, et al. (1997) Virology, 239: 226-37, as further evidenced by Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67, Qiu, et al. (1998) Human Gene Therapy, 9(4): 507-20 (ABSTRACT ONLY); and Hodgeson (1996) Nature Biotechnology, 14: 339-342; Song, et al. (2000) Oncology Reports, 7(1): 119-24; Porter, et al. (1998) Journal of Virology, 72(6): 4832-40; Saeki, et al. (1997) Human Gene Therapy, 8(17): 2133-41; Kaneko, et al. (1996) Cancer Letters 107: 211-15; Kaneko, et al. (1996) Cancer Letters, 105: 39-44; Shimura, et al. (1985) Virology, 144(1): 268-72, and as further evidenced by U.S. Patent No. 7,091,030 to Setiawan, are withdrawn.

To wit, the amendments now require at least the administration of 6MPDR.

Rejections based on PNP/6MPDR

In light of the amendments, the rejections of Claims 1 and 3 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,159,467 to Chung, et al., and Khatri, et al. (1997) Virology, 239: 226-37, as further evidenced by Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67), Qiu, et al. (1998) Human Gene Therapy, 9(4): 507-20 (ABSTRACT ONLY); and Hodgeson (1996) Nature Biotechnology, 14: 339-342; Song, et al. (2000) Oncology Reports, 7(1): 119-24; Porter, et al. (1998) Journal of Virology, 72(6): 4832-40; Saeki, et al. (1997) Human Gene Therapy, 8(17): 2133-41; Kaneko, et al. (1996) Cancer Letters 107: 211-15; Kaneko, et al. (1996) Cancer Letters, 105: 39-44; Shimura, et al. (1985) Virology, 144(1): 268-72 and as further evidenced by U.S. Patent No. 7,091,030 to Setiawan, as applied to claims 1-4, 9, 10, 12-14, 16, 17, 22, 23, and 25-27 above, and further in view of Martiniello-Wilks, et al. (1998) Human Gene Therapy, 9(11): 1617-26 (ABSTRACT ONLY), are withdrawn.

To wit, the claims now require at least the probasin promoter and a transcriptional enhancer.

Rejections based on Further comprising an AdV type 5 Fiber

In light of the amendments, the rejections of Claims 1 and 3 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,159,467 to Chung, et al., and Khatri, et al. (1997) Virology, 239: 226-37, as further evidenced by Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene

Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67), Qui, et al. (1998) Human Gene Therapy, 9(4): 507-20 (ABSTRACT ONLY); and Hodgeson (1996) Nature Biotechnology, 14: 339-342; Song, et al. (2000) Oncology Reports, 7(1): 119-24; Porter, et al. (1998) Journal of Virology, 72(6): 4832-40; Saeki, et al. (1997) Human Gene Therapy, 8(17): 2133-41; Kaneko, et al. (1996) Cancer Letters 107: 211-15; Kaneko, et al. (1996) Cancer Letters, 105: 39-44; Shimura, et al. (1985) Virology, 144(1): 268-72, as applied to claims 1-4, 9, 10, 12, 16, 17, 22, 23, and 25 above, and further in view of Martiniello-Wilks, et al. (1998) Human Gene Therapy, 9(11): 1617-26 (ABSTRACT ONLY), and as further evidenced by U.S. Patent No. 7,091,030 to Setiawan as applied to claims 1-4, 9-14, 16, 17, and 22-27 above, and further in view of Xu, et al. (1998) Virology, 248: 156-63, are withdrawn.

To wit, the claims now require at least the probasin promoter and transcriptional enhancer.

Art Rejections of Specific Virus Claims

In light of the amendments, the rejection of Claim 1 under 35 U.S.C. 103(a) as being unpatentable over any of the above-listed rejections as applied to those claims applicable to each above, and further in view of Pramudji, et al. (2001) Clinical Cancer Research, 7: 4272-79, Krohne, et al. (2001) Hepatology, 34: 511-18, and Ramasamy, et al. (1999) Biochimica et Biophysica Acta, 1453: 1-13, is withdrawn.

To wit, due to the amendments, the rejection is simply no longer required, as the specific atadenoviruses are no longer claimed. Hence, in order to avoid confusion in the Record, the rejection is withdrawn in favor of maintaining other rejections.

Rejections Maintained and Applied for Reasons of Record

Art Rejections Utilizing the Probasin Promoter and/or PSA Enhancer

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 29, and 30 remain and/or are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,159,467 to Chung, et al., and Khatri, et al. (1997) Virology, 239: 226-37, as further evidenced by Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67), Qui, et al. (1998) Human Gene Therapy, 9(4): 507-20 (ABSTRACT ONLY); and Hodgeson (1996) Nature Biotechnology, 14: 339-342; Song, et al. (2000) Oncology Reports, 7(1): 119-24; Porter, et al. (1998) Journal of Virology, 72(6): 4832-40; Sacki, et al. (1997)

Human Gene Therapy, 8(17): 2133-41; Kaneko, et al. (1996) Cancer Letters 107: 211-15; Kaneko, et al. (1996) Cancer Letters, 105: 39-44; Shimura, et al. (1985) Virology, 144(1): 268-72, and further in view of Martiniello-Wilks, et al. (1998) Human Gene Therapy, 9(11): 1617-26 (ABSTRACT ONLY), and as further evidenced by U.S. Patent No. 7,091,030 to Setiawan as applied to claims 1-4, 9-14, 16, 17, and 22-27 above, and further in view of U.S. Patent No. 6,197,293 to Henderson, et al., for reasons of record.

Also:

Claims 1, 3, 29, and 30 remain or are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,159,467 to Chung, et al., and Khatri, et al. (1997) Virology, 239: 226-37, as further evidenced by Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67), Qui, et al. (1998) Human Gene Therapy, 9(4): 507-20 (ABSTRACT ONLY); and Hodgeson (1996) Nature Biotechnology, 14: 339-342; Song, et al. (2000) Oncology Reports, 7(1): 119-24; Porter, et al. (1998) Journal of Virology, 72(6): 4832-40; Sacki, et al. (1997) Human Gene Therapy, 8(17): 2133-41; Kaneko, et al. (1996) Cancer Letters 107: 211-15; Kaneko, et al. (1996) Cancer Letters, 105: 39-44; Shimura, et al. (1985) Virology, 144(1): 268-72, and further in view of Martiniello-Wilks, et al. (1998) Human Gene Therapy, 9(11): 1617-26 (ABSTRACT ONLY), and further in view of Xu, et al. (1998) Virology, 248: 156-63 and as

further evidenced by U.S. Patent No. 7,091,030 to Setiawan, and further in view of U.S. Patent No. 6,197,293 to Henderson, et al., for reasons of record.

For purposes of clarity, because the previous rejections were provided through chains of added references, the rejections are now rewritten in one confluent rejection to make clear, for possible future appeal, the substance of the rejections.

The claims are encompass any ovine atadenovirus (atadenoviruses are a genus of adenoviruses that cover mammalian and ovine adenoviruses), such ovine atadenovirus comprising a probasin promoter (see objection to claim above for further explanation), and a transcriptional enhancer sequence (see rejection for lack of clarity above), operatively linked to a purine nucleoside phosphorylase enzyme and a CS87 or CS60 lipid of specific formulae (which determine the CS87 and CS60 known in the Art). The compositions may further comprise 6MPDR or fludarabine (which are nucleoside analogs which are known in the art to act with specific purine phosphorylase enzymes to produce toxins). These compositions are utilized in the method claims to treat a solid tumor in a subject, by delivery of the engineered atadenoviruses to the tumor with a CS87 or CS60 lipid, and also administration of the 5PMDR or fludarabine.

Chung teaches the use of recombinant adenovirus vectors comprising a promoter operatively to a thymidine kinase encoding region, for suicide gene therapy of, *inter alia*, prostate cancer, and several other forms of cancer (e.g., ABSTRACT). Chung teaches direct

administration of such vectors to the cancer (ABSTRACT), which may be a solid tumor (e.g., cols. 2-3, paragraph bridging). Further, Chung teaches the advantage of tissue-specific promoters (e.g., cols. 2-3, paragraph bridging).

Khatri teaches that the Ovine Adenovirus prototype, OAV287, can infect many human cell cancer types, including at least one prostate cancer (e.g., ABSTRACT).

Henderson teaches one such specific promoter and enhancer is a probasin promoter and PSA enhancer (e.g., col. 8, paragraph 3).

Martiniello-Wilks teaches the use of PNP/6MPDR in similar methods of treating cancer cells, including prostate cancer cells (e.g., ABSTRACT).

Xu teaches that modifying an ovine atadenovirus, to comprise the human type 5 adenovirus cell-binding domain, increases the breadth of prostate cancer types that could be transformed by the adenovirus (e.g., ABSTRACT).

However, the aforementioned art does not teach the specific further use of cationic lipids in the composition, or for administration as a composition, with an atadenovirus.

On the other hand, a wide range of art on adenoviruses at the time of invention taught that the use of cationic liposomes would increase the transfection efficiency of adenoviruses (e.g., Lee, et al. (2000) Cancer Gene Therapy, 7(10): 1329-35; Ryuke, et al. (2000) Neurol. Med. Chir. (Tokyo) 40: 256-60; Ma, et al. (2002) Gene Therapy, 9: 176-82; Dunphy, et al. (1999) Human Gene Therapy, 10: 2407-17; Sung, et al. (2000) Anticancer Research, 20(3A): 1653-66; Meunier-Durmort, et al. (1996) European Journal of Biochemistry, 237: 660-67; and Natsume, et al. (2000) Japanese Journal of Cancer Research, 91(4): 363-67). Furthermore, such enhancement

is distinct from the fiber receptor and alpha(v) integrin pathways of entry (e.g., Qiu, et al. (1998) Human Gene Therapy, 9(4): 507-20 (ABSTRACT ONLY)).

Moreover, an even wider range of art demonstrates that the effect of cationic liposomes to enhance transfection efficiency of viral vector particles goes far beyond adenovirus vectors (e.g., Hodgeson (1996) Nature Biotechnology, 14: 339-342; Song, et al. (2000) Oncology Reports, 7(1): 119-24; Porter, et al. (1998) Journal of Virology, 72(6): 4832-40; Saeki, et al. (1997) Human Gene Therapy, 8(17): 2133-41; Kaneko, et al. (1996) Cancer Letters 107: 211-15; Kaneko, et al. (1996) Cancer Letters, 105: 39-44; Shimura, et al. (1985) Virology, 144(1): 268-72).

Still further, Setiawan teaches the specific CS87 (e.g., CLAIMS), as well all the genera to which CS60 belongs, as cationic lipids, as well as the additional advantage of the presence of such lipids, as being stabilizers of the viruses, including atadenoviruses (e.g., CLAIMS).

Hence, at the time of invention the Artisan would have been motivated to perform the methods, and make the compositions, as such compositions would be made to perform the methods, *in vitro,* as well as *in vivo*. The Artisan would have been motivated to substitute the adenovirus with the atadenovirus as such atadenovirus performs the equivalent function of transfecting prostate cancer cells. The Artisan would have been motivated to utlize the probasin promoter and enhancer to drive expression of the gene, as these elements were already known in the Art to be tissue specific for prostate cancer cells. The Artisan would have been motivated to utilize the PNP gene with 6MPDR as such suicide gene therapy had already been shown to be functionally equivalent in similar methods. Further, the Artisan would be motivated to modify the viruses to comprise the human type 5 cell-binding domain of adenovirus in order to increase

the transformation efficiency of prostate cancer cells. Moreover, the Artisan would have been motivated to utilize the CSO 87 and CSO 60 (now claimed as CS87 and CS60 -- which are simply alternative designations of the same compounds) along with the vectors, as it was well demonstrated by the Art that such cationic lipids could not only increase transfection efficiency, but also serve as a cryoprotectant. Moreover, the Artisan would have had a reasonable expectation of success, as the various permutations are simply ones of substitution of already known functional equivalents, and in the case of the lipids, it had already been shown that the lipids would increase transfection efficiency.

Moreover, the compositions are even obvious without the requirement of *in vivo* function, as they could be utilized to transform cancer cells *in vitro*. Hence, the simple use of the lipids would be obvious as Setiwan teaches it as a cryoprotectant. Moreover, the Artisan would have a reasonable expectation of success, as Setiwan teaches the lipids work, and the other elements are functional equivalents.

Response to Argument – All Previous Art Rejections of Record

Applicant's argument of 3/7/08 have been fully considered but are not found persuasive.

Applicant makes several arguments that the rejections do not contain limitations found in the claims, and hence, the claims are not properly rejected (throughout argument, e.g., p. 7, paragraph 3).

Such is persuasive to the extent that Applicant's claims were not rejected on the basis of various limitations, except that of the enhancer. In such case, Applicant's present claims do not

encompass simply the argued enhancer, but any enhancer (see rejection for lack of clarity). Further, one rejection set has been withdrawn, as Applicant no longer claims the specific adenoviruses, and maintaining the rejections would simply lead to more confusion of the issues in any possible appeal. The balance of the rejections were proper and made obvious the previously-rejected claims.

Applicant argues that the results obtained could not have been predicted based on four pieces of cited Art (Wang, et al. (2004) Gene Therapy, 11: 1559-67; Mariniello-Wilkes, et al. (2004) Journal of Gene Medicine, 6: 43-54; Mariniello-Wilkes, et al. (2004) Journal of Gene Medicine, 6: 1343-57; and Fasbender, et al. (1997) Journal of Biological Chemistry, 272(10): 6479-89), that unexpected results are obtained in Applicant's claimed methods, which comprise unexpectedly enhanced activity with the claimed composition and method, and hence, these unexpected results preclude obviousness-type rejections (pp. 7-8). These same arguments are repeated throughout the argument supplied by Applicant.

Such is not persuasive. While each of these pieces of Art demonstrates various novel methods, none of them demonstrate that the methods were not obvious. Moreover, the enhanced infectivity in the presence of the cationic lipids was quite expected, as is demonstrated by the prior art utilized in the rejection, such art being prior to the date of invention by Applicant. Hence, broad argument to unexpected results does not overcome the present rejections. Finally, with respect to the compositions, Setiawan demonstrates another use for these compositions, as a cryoprotected vector, and hence, unexpected results to *in vivo* use are not required of the claims, and hence, Applicant's arguments fail to address this other use of the compositions as claimed, for storage of vectors to transform prostate cancer cells *in vitro*.

At the core of the argument between the Examiner and Applicant, is the question raised in light of the Art cited: whether the Artisan would have had a reasonable expectation of success to increase transfection efficiency due to the presence of the cationic lipids claimed, and therefore whether or not the results are unexpected. While the Art may argue that Applicant's claimed invention is novel, the claims are rejected on the basis of obviousness, and hence, the simple citation of similar embodiments may demonstrate novelty, they certainly do not go to obviousness-type rejections. Applicant argues, citing such art (which the Examiner is making of record with this Action), that it is also non-obvious because the Art demonstrates a result that is unexpected. However, the Exmainer disagrees with Applicant's analysis. The Art cited by the Examiner demonstrates, as is shown in the rejections themselves, that the Artisan would have understood that cationic lipids increase the transfection efficiency of adenoviruses, further the Art demonstrates that such increases in transfection efficiency is not due to the specific cell receptors of the adenovirus, and lastly, that more art demonstrates that such cationic lipids work to increase the transfection efficiency of completely unrelated viruses. Hence, the Examiner argues, the mechanism of action appears to be one that is not dependent on viral type, and certainly not on adenoviral type, and there is no art that argues against such mechanisms not working on the subtype of adenoviruses of ovine atadenoviruses. Therefore, it would appear to the Artisan that such methods and compositions are obvious. Also, the compositions are further obvious for other reasons: for cyroprotection of the compositions for use *in vitro*.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Acting Examiner of Art Unit 1633